

WHAT IS CLAIMED IS:

1. A cocrystal comprising a salt and a neutral guest, wherein the salt comprises an active agent and a counterion, wherein the guest is a carboxylic acid having at least three carbon atoms, and the cocrystal is not a solvate.

2. The cocrystal of claim 1, wherein the guest is a carboxylic acid having at least four carbon atoms.

3. The cocrystal of claim 1, wherein the guest is selected from the group consisting of the guests set forth in Table 1.

4. The cocrystal of claim 1, wherein the guest is selected from the group consisting of the guests set forth in Table 2.

5. The cocrystal of claim 1, wherein the guest is selected from the group consisting of the guests set forth in Table 3.

6. The cocrystal of claim 1, wherein the guest is a carboxylic acid selected from the group consisting of:

sorbic acid;

L-(+)-tartaric acid;

citric acid;

benzoic acid;

aspirin;

lactic acid;

fumaric acid;

(S) - (+) - arginine;  
glycine;  
(S) - (-) - histidine;  
(S) - (+) - lysine;  
DL-tartaric acid;  
(S) - (-) - phenylalanine;  
(S) - (-) - tyrosine;  
phenylacetic acid;  
adipic acid;  
pyruvic acid;  
succinic acid;  
niacin;  
4-aminobenzoic acid;  
o-methylbenzoic acid;  
valeric acid;  
maleic acid;  
3-methylbutanoic acid;  
L-glutamic acid;  
2,4-dihydroxybenzoic acid;  
3-phenylpropionic acid;  
isocaproic acid;  
(L) - (+) - isoleucine;  
L-malic acid;  
L-2-aminopropionic acid;  
L-glutamine;  
L-hydroxyproline  
L-proline  
L-serine;  
L-threonine;  
L-valine;  
Phenoxyacetic acid  
2-ethylbutyric acid;

L-leucine;  
L-asparagine;  
levulinic acid;  
(S)-(-)-cysteine;  
DL-aspartic acid;  
4-hydroxybenzoic acid;  
diphenylacetic acid;  
glutaric acid;  
0-toluic acid;  
pivalic acid;  
DL-malic acid;  
beta-alanine;  
(S)-(-)-tryptophan;  
malonic acid;  
mandelic acid;  
glycolic acid;  
terephthalic acid;  
1-hydroxy-2-naphthoic acid;  
4-aminosalicylic acid;  
orotic acid;  
gallic acid;  
gentisic acid;  
pamoic acid;  
n-butyric acid;  
n-hexanoic acid;  
2-furancarboxylic acid;  
p-acetamidobenzoic acid;  
galactaric acid;  
lactobionic acid;  
2-mercaptobenzoic acid;  
3-cyclopentylpropionic acid;  
DL-lysine;

cinnamic acid;  
dichloroacetic acid;  
octanoic acid;  
isobutyric acid;  
anisic acid;  
enanthoic acid;  
hippuric acid;  
tiglic acid;  
cyclohexanecarboxylic acid;  
m-methoxybenzoic acid;  
D-(+)-camphoric acid; and  
cyclohexylacetic acid.

7. The cocrystal of claim 1, wherein the guest is a carboxylic acid selected from the group consisting of:

ascorbic acid;  
glucoheptonic acid;  
sebacic acid;  
alginic acid;  
cyclamic acid;  
ethane-1,2-disulfonic acid;  
2-hydroxyethanesulfonic acid;  
2-oxo-glutaric acid;  
naphthalene-1,5-disulfonic acid;  
nicotinic acid;  
pyroglutamic acid; and  
4-acetamidobenzoic acid.

8. The cocrystal of claim 1, wherein the guest is selected from the group consisting of benzoic acid, succinic acid, and fumaric acid.

9. The cocrystal of claim 1, wherein the counterion is a halide.

10. The cocrystal of claim 9, wherein the counterion is chloride.

11. The cocrystal of claim 1, wherein the counterion is a positive counterion.

12. The cocrystal of claim 1, wherein the active agent comprises a secondary or tertiary amine, and said amine forms a salt with the counterion.

13. The cocrystal of claim 11, wherein the amine is a tertiary amine.

14. The cocrystal of claim 1, wherein the active agent comprises an active pharmaceutical ingredient.

15. The cocrystal of claim 1, wherein the active agent comprises a nutraceutical.

16. The cocrystal of claim 1, wherein the active agent comprises an agricultural chemical.

17. The cocrystal of claim 1, wherein the active agent comprises a pigment.

18. The cocrystal of claim 1, wherein the active agent comprises a dye.

19. The cocrystal of claim 1, wherein the active agent comprises an explosive.

20. The cocrystal of claim 1, wherein the active agent comprises a polymer additive.

21. The cocrystal of claim 1, wherein the active agent comprises a lubricant additive.

22. The cocrystal of claim 1, wherein the active agent comprises a photographic chemical.

23. A cocrystal comprising a salt and a neutral guest, wherein the salt comprises an active agent and a counterion, wherein the guest is a strong hydrogen bond donor and is selected from the guests set forth in Table 3.

24. The cocrystal of claim 23, wherein the guest is a carboxylic acid having at least four carbon atoms.

25. The cocrystal of claim 23, wherein the guest is selected from the group consisting of the guests set forth in Table 1.

26. The cocrystal of claim 23, wherein the guest is selected from the group consisting of the guests set forth in Table 2.

27. The cocrystal of claim 23, wherein the guest is a carboxylic acid selected from the group consisting of:

sorbic acid;

L-(+)-tartaric acid;

citric acid;  
benzoic acid;  
aspirin;  
lactic acid;  
fumaric acid;  
(S) - (+) - arginine;  
glycine;  
(S) - (-) - histidine;  
(S) - (+) - lysine;  
DL-tartaric acid;  
(S) - (-) - phenylalanine;  
(S) - (-) - tyrosine;  
phenylacetic acid;  
adipic acid;  
pyruvic acid;  
succinic acid;  
niacin;  
4-aminobenzoic acid;  
o-methylbenzoic acid;  
valeric acid;  
maleic acid;  
3-methylbutanoic acid;  
L-glutamic acid;  
2,4-dihydroxybenzoic acid;  
3-phenylpropionic acid;  
isocaproic acid;  
(L) - (+) - isoleucine;  
L-malic acid;  
L-2-aminopropionic acid;  
L-glutamine;  
L-hydroxyproline  
L-proline

L-serine;  
L-threonine;  
L-valine;  
Phenoxyacetic acid  
2-ethylbutyric acid;  
L-leucine;  
L-asparagine;  
levulinic acid;  
(S)-(-)-cysteine;  
DL-aspartic acid;  
4-hydroxybenzoic acid;  
diphenylacetic acid;  
glutaric acid;  
o-toluic acid;  
pivalic acid;  
DL-malic acid;  
beta-alanine;  
(S)-(-)-tryptophan;  
malonic acid;  
mandelic acid;  
glycolic acid;  
terephthalic acid;  
1-hydroxy-2-naphthoic acid;  
4-aminosalicylic acid;  
orotic acid;  
gallic acid;  
gentisic acid;  
pamoic acid;  
n-butyric acid;  
n-hexanoic acid;  
2-furancarboxylic acid;  
p-acetamidobenzoic acid;



galactaric acid;  
lactobionic acid;  
2-mercaptobenzoic acid;  
3-cyclopentylpropionic acid;  
DL-lysine;  
cinnamic acid;  
dichloroacetic acid;  
octanoic acid;  
isobutyric acid;  
anisic acid;  
enanthoic acid;  
hippuric acid;  
tiglic acid;  
cyclohexanecarboxylic acid;  
m-methoxybenzoic acid;  
D-(+)-camphoric acid; and  
cyclohexylacetic acid.

28. The cocrystal of claim 23, wherein the guest is a carboxylic acid selected from the group consisting of:

ascorbic acid;  
glucoheptonic acid;  
sebacic acid;  
alginic acid;  
cyclamic acid;  
ethane-1,2-disulfonic acid;  
2-hydroxyethanesulfonic acid;  
2-oxo-glutaric acid;  
naphthalene-1,5-disulfonic acid;  
nicotinic acid;  
pyroglutamic acid; and  
4-acetamidobenzoic acid.

29. The cocrystal of claim 23, wherein the guest is selected from the group consisting of benzoic acid, succinic acid, and fumaric acid.

30. The cocrystal of claim 23, wherein the counterion is a halide.

31. The cocrystal of claim 30, wherein the counterion is chloride.

32. The cocrystal of claim 23, wherein the active agent comprises a secondary or tertiary amine, and said amine forms a salt with the counterion.

33. The cocrystal of claim 32, wherein the amine is a tertiary amine.

34. The cocrystal of claim 23, wherein the active agent comprises an active pharmaceutical ingredient.

35. The cocrystal of claim 23, wherein the active agent comprises a nutraceutical.

36. The cocrystal of claim 23, wherein the active agent comprises an agricultural chemical.

37. The cocrystal of claim 23, wherein the active agent comprises a pigment.

38. The cocrystal of claim 23, wherein the active agent comprises a dye.

39. The cocrystal of claim 23, wherein the active agent comprises an explosive.

40. The cocrystal of claim 23, wherein the active agent comprises a polymer additive.

41. The cocrystal of claim 23, wherein the active agent comprises a lubricant additive.

42. The cocrystal of claim 23, wherein the active agent comprises a photographic chemical.

43. A cocrystal comprising a salt and a neutral guest, wherein the salt comprises an active agent and a counterion, and wherein the counterion is not a chloride ion.

44. The cocrystal of claim 43, wherein the salt is formed from the active agent and a mineral acid, and the mineral acid provides the counterion.

45. The cocrystal of claim 43, wherein the salt is formed from the active agent and an inorganic acid, and the inorganic acid provides the counterion.

46. The cocrystal of claim 43, wherein the salt is formed from the active agent and an acid selected from the group consisting of:

sulfuric acid;

phosphoric acid;

hydrobromic and;

nitric acid;  
pyrophosphoric acid;  
methanesulfonic acid;  
thiocyanic acid;  
naphthalene-2-sulfonic acid;  
1,5-naphthalenedisulfonic acid;  
cyclamic acid;  
p-toluenesulfonic acid;  
maleic acid;  
L-aspartic acid;  
2-hydroxy-ethanesulfonic acid;  
glycerophosphoric acid;  
ethanesulfonic acid; and  
hydroiodic acid,  
and the acid provides the counterion.

47. The cocrystal of claim 43, wherein the guest is a phosphate.

48. The cocrystal of claim 43, wherein the guest is a bromide.

49. The cocrystal of claim 43, wherein the guest is a carboxylic acid having at least three carbon atoms.

50. The cocrystal of claim 43, wherein the guest is selected from the group consisting of the guests set forth in Table 1.

51. The cocrystal of claim 43, wherein the guest is selected from the group consisting of the guests set forth in Table 2.

52. The cocrystal of claim 43, wherein the guest is selected from the group consisting of the guests set forth in Table 3.

53. The cocrystal of claim 43, wherein the guest is a carboxylic acid selected from the group consisting of:

- sorbic acid;
- L-(+)-tartaric acid;
- citric acid;
- benzoic acid;
- aspirin;
- lactic acid;
- fumaric acid;
- (S)-(+) -arginine;
- glycine;
- (S)-(-)-histidine;
- (S)-(+) -lysine;
- DL-tartaric acid;
- (S)-(-)-phenylalanine;
- (S)-(-)-tyrosine;
- phenylacetic acid;
- adipic acid;
- pyruvic acid;
- succinic acid;
- niacin;
- 4-aminobenzoic acid;
- o-methylbenzoic acid;
- valeric acid;
- maleic acid;
- 3-methylbutanoic acid;
- L-glutamic acid;

2,4-dihydroxybenzoic acid;  
3-phenylpropionic acid;  
isocaproic acid;  
(L) - (+) -isoleucine;  
L-malic acid;  
L-2-aminopropionic acid;  
L-glutamine;  
L-hydroxyproline  
L-proline  
L-serine;  
L-threonine;  
L-valine;  
Phenoxyacetic acid  
2-ethylbutyric acid;  
L-leucine;  
L-asparagine;  
levulinic acid;  
(S) - (-) -cysteine;  
DL-aspartic acid;  
4-hydroxybenzoic acid;  
diphenylacetic acid;  
glutaric acid;  
o-toluic acid;  
pivalic acid;  
DL-malic acid;  
beta-alanine;  
(S) - (-) -tryptophan;  
malonic acid;  
mandelic acid;  
glycolic acid;  
terephthalic acid;  
1-hydroxy-2-naphthoic acid;

4-aminosalicylic acid;  
orotic acid;  
gallic acid;  
gentisic acid;  
pamoic acid;  
n-butyric acid;  
n-hexanoic acid;  
2-furancarboxylic acid;  
p-acetamidobenzoic acid;  
galactaric acid;  
lactobionic acid;  
2-mercaptobenzoic acid;  
3-cyclopentylpropionic acid;  
DL-lysine;  
cinnamic acid;  
dichloroacetic acid;  
octanoic acid;  
isobutyric acid;  
anisic acid;  
enantioic acid;  
hippuric acid;  
tiglic acid;  
cyclohexanecarboxylic acid;  
m-methoxybenzoic acid;  
D-(+)-camphoric acid; and  
cyclohexylacetic acid.

54. The cocrystal of claim 43, wherein the guest is a carboxylic acid selected from the group consisting of:

ascorbic acid;  
glucoheptonic acid;  
sebacic acid;

alginic acid;  
cyclamic acid;  
ethane-1,2-disulfonic acid;  
2-hydroxyethanesulfonic acid;  
2-oxo-glutaric acid;  
naphthalene-1,5-disulfonic acid;  
nicotinic acid;  
pyroglutamic acid; and  
4-acetamidobenzoic acid.

55. The cocrystal of claim 43, wherein the guest is selected from the group consisting of benzoic acid, succinic acid, and fumaric acid.

56. A cocrystal comprising a guest and an active agent, wherein the guest is an amine salt which provides a counterion, and the active agent is a carboxylic acid.

57. A method of generating a cocrystal comprising:  
adding a minor amount of an organic solvent separately to a solid active agent and a guest;  
melting the active agent to form a solution of the API and the organic solvent;  
melting the guest to form a solution of the guest and the organic solvent;  
forming a mixture of the two solutions; and  
solidifying the resulting mixture to form a cocrystal of the active agent and the guest.

58. A method of preparing a cocrystal of a salt of an active agent and a guest, said method comprising:



selecting a salt of an active agent, wherein said salt comprises the active agent and a counterion;

theorizing coordination of the counterion by hydrogen bond interactions within said crystal;

selecting a guest to coordinate more strongly with the counterion than the coordination within said crystal;

preparing a solution, melt or physical mixture comprising the active agent, the counterion, and the guest;

subjecting the solution or melt to a crystallization process, or the physical mixture to grinding;

forming a cocrystal comprising the salt of the active agent and the guest, wherein the counterion is coordinated with the guest through strong hydrogen bond interactions.

59. The method of claim 58, wherein the counterion is a negative counterion, and the guest is a stronger hydrogen bond donor for at least one coordination site than the active agent.

60. The method of claim 58, wherein the crystal contains at least one C-H hydrogen bond donor with the counterion, and the guest replaces said at least one C-H hydrogen bond donor with at least one O-H hydrogen bond donor.

61. A method of modifying one or more physical properties of a drug formulation, the drug formulation comprising an API, said method comprising:

forming cocrystals of the API with a plurality of guests;

measuring at least one physical property of said cocrystals;

assessing the effect of each guest on said at least one physical property; and

preparing the drug formulation from one of said cocrystals having a desired physical property.

62. The method of claim 61, wherein the API is a neutral API.

63. The method of claim 61, wherein the API is provided as a salt.

64. A method of preparing a cocrystalline pharmaceutical composition, said method comprising:

obtaining a salt of an active pharmaceutical ingredient, wherein the salt has a negative counterion other than chloride;

substituting chloride for the negative counterion in the obtained salt; and

cocrystallizing the substituted salt with a suitable guest.

65. A method of preparing a cocrystal from a hydrate, wherein the cocrystal comprises a salt and a neutral guest, and wherein the salt comprises an active agent and a counterion, said method comprising:

providing a hydrate of the salt comprising water of hydration;

selecting a guest to coordinate with the counterion;

preparing a solution, melt or physical mixture comprising the hydrate and the guest;

subjecting the solution or melt to a crystallization process or the physical mixture to grinding; and

forming a cocrystal comprising the salt of the active agent and the guest.

66. The method of claim 65, wherein the guest coordinates more strongly with the counterion than the water of hydration coordinates with the counterion.

67. A method of preparing a cocrystal from a solvate, wherein the cocrystal is not a solvate and comprise a salt and a neutral guest, and wherein the salt comprises an active agent and a counterion, said method comprising:

providing a solvate of the salt comprising solvent molecules coordinated with the salt;

selecting a guest to coordinate more strongly with the counterion than the solvent;

preparing a solution, melt or physical mixture comprising the solvate and the guest;

subjecting the solution or melt to a crystallization process or the physical mixture to grinding; and

forming a cocrystal comprising the salt of the active agent and the guest.

68. The method of claim 67, wherein the guest coordinates more strongly with the counterion than the solvent water of hydration coordinates with the counterion.